LYMErix® Safety Data Reported to the Vaccine Adverse Event Reporting System (VAERS) from December 21, 1998 through October 31, 2000

Introduction

At the time of licensure, safety data were available for LYMErix® in 6,478 individuals who had received a total of 18,047 doses of vaccine. As for any drug or biologic product, rare events or associations with other health problems that were not seen during pre-licensure clinical trials may occur post-licensure. As one approach to monitor the number and type of adverse events following vaccination with LYMErix®, we analyzed reports of adverse events following Lyme disease vaccination submitted to the federal Vaccine Adverse Event Reporting System (VAERS).

Established in 1990 and operated collaboratively by the FDA and the CDC, VAERS receives over 10,000 adverse event reports annually. Reports are submitted by vaccine providers, other health care givers, vaccine recipients and relatives of recipients, vaccine manufacturers, attorneys, and other interested parties. Deaths and serious reports (defined as an event that resulted in life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability) are followed up by telephone to obtain additional information about the event and the patient's prior medical history.

Passive surveillance systems such as VAERS are subject to many limitations. True associations will inevitably be underreported, to an unknown extent. Equally problematic, temporal associations will be reported, with little data to evaluate any causal connection with the vaccine. Inadequate denominator data are available to determine incidence rates; although the number of doses distributed is available to the FDA we do not know the number of doses actually administered, nor the demographic distribution of those receiving the vaccine. Reporting of unconfirmed diagnoses is common, and on follow-up

initially reported diagnoses are commonly found to be inaccurate. For purposes of evaluating the possible causal relationship between an event and a vaccination, a particularly important limitation is the lack of a direct and unbiased comparison group from which to determine the incidence of adverse events among people who have not been vaccinated.

Because of these limitations, it is usually not possible to determine causal associations between vaccines and adverse events from VAERS reports, unless the event is a well-recognized reaction (e.g. injection site reaction) or confirmatory laboratory results are included (e.g. vaccine strain virus detected in paralytic polio case). Signals of possible causally linked adverse events are identified by finding unexpected patterns in age, gender, dose number, and time to onset, or substantial numbers of "positive rechallenge" reports. Additional criteria such as biological plausibility, the presence of pre-existing conditions, and concomitant illnesses, medication usage, or other exposures need to be examined to further determine the plausibility of an association between a vaccine and an adverse event. Signals identified as plausibly linked to the vaccine almost always require confirmation using a traditional epidemiological or other (e.g. laboratory) study.

An important additional limitation of VAERS is the lack of standardization of diagnoses. Reports are processed by non-physician nosologists, without the benefit of standardized case definitions, using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) to describe the adverse event in a computerized data bank. Report coding depends on the use of certain words or phrases. This results in the use of the same COSTART term for reports with different degrees of diagnostic precision. For example, a report may simply say, "I developed arthritis after I received the vaccine", without any other supporting medical information. Such a report would likely be coded as

"arthritis", as would a report that included a complete medical record documenting joint swelling and tenderness by a physician examination. As a result, coding terms must be interpreted very cautiously. A copy of the VAERS reporting form is attached to indicate the standard data collected.

In spite of these limitations, use of VAERS data has allowed for the detection of previously unrecognized or rare reactions to vaccines (e.g. intussusception after rotavirus vaccine) and has suggested the need for further study of other reactions (e.g. hair loss after routine immunizations).

We analyzed all reports of adverse events following administration of LYMErix® received by VAERS from December 28, 1998 through October 31, 2000. Approximately 1,449,203 doses of the vaccine were distributed through July 31, 2000. We focused on reports of arthritis and facial paralysis because these have been associated with Lyme disease. Hypersensitivity reactions were also evaluated because they are reported following many routine immunizations. We also examined adverse events in people with a self-reported DR4 HLA type, history of Lyme disease, and diagnosis of Lyme disease subsequent to vaccination.

Analysis of VAERS data

A total of 1,048 adverse events following LYMErix® administration was reported to VAERS from December 21, 1998 through October 31, 2000, representing about 0.07% of all doses distributed. Most adverse events (1,026, 98%), occurred in people who received only LYMErix® (i.e. no simultaneous administration of any other vaccine). Adverse events were reported in people from 5 to 82 years of age as shown in figure 1, with a median age of 57 (interquartile range: 40-57) and mean of 48 years. Seven and 34 adverse events were reported in people under age 15 and over age 70, respectively, the lower and upper age bound for recommended use of the vaccine. Adverse events

were reported for 522 males (53%) and 469 females (47%) and gender was not available for 57 reports. Data on age and gender distribution of vaccine recipients are not available.

The majority of the 739 reported events for which time to onset was available (423/739, 57%) occurred either on the day of vaccination (36%), or within the following two days (21%), as shown in figure 2. This pattern is typical for most vaccine adverse events reported to VAERS. Information on dose sequence was available for 1,007 (96%) of the reported events and is shown in figure 3. More than half (540, 54%) of the events with a known dose occurred after administration of the first dose of LYMErix®. The ten most common adverse events reported to VAERS following LYMErix® are shown in Table 1. The bolded events were found to be associated with the vaccine in the pre-licensure trial.

Four deaths were reported following administration of LYMErix®. One of the deceased was a 63-year-old man who died one day after receiving his first dose of LYMErix®. The cause of his death, based on an autopsy, was found to be hypertensive cardiovascular disease. A second death was reported in a 54-year-old man, who died 3 days after receiving his second dose of LYMErix®. The autopsy report revealed the cause of death to be cardiovascular disease and hypertension. The third death reported to VAERS was in a 43-year-old man, who committed suicide 7 months after receiving his second dose of LYMErix®, after developing arthritic and neurological symptoms that the reporter attributed to LYMErix®. Approximately one month after the second dose he developed "abdominal soreness, testicular pain, and tightness in the lower back". His symptoms and signs worsened to include paresthesias, fatigue, muscle atrophy, weight loss, difficulty walking, weakness, vision changes, depression, difficulty sleeping, and poor concentration. An extensive medical evaluation, including MRI of spine and hips and EMG, was non-diagnostic. The autopsy report did not reveal any clear pathology

that would explain his arthritic and neurologic problems, but the extent to which these conditions were evaluated was not indicated in the report. The fourth reported death was a 69-year-old woman who developed cough, dyspnea, and fever and was found to have anemia and thrombocytopenia 7 months after the first dose. She subsequently was found to have splenic infarcts and underwent splenectomy, then developed severe pancytopenia, and died 6 months later some time after receiving the third dose of the vaccine (the exact time is unknown). An autopsy was not conducted in this case; the cause of death was reported as myelofibrosis.

The FDA considers a serious event reported to VAERS to be one that resulted in life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability. The coding of the level of seriousness of an event is based on the information provided by the reporter on the VAERS form. Only a small minority (85, 8%) of the reported adverse events following LYMErix® administration were classified as serious, according to this definition. Of these 85 serious events, all but one report provided details about the symptoms or signs associated with the event. These events are summarized in table 2. We have not identified any clear patterns of unexpected events in these reports. The neurological events were diverse and no single condition predominated. Events involving cerebral ischemia (3 cerebrovascular accidents, 2 transient ischemic attacks) were reported, but these events are relatively common in the older age group (median age 62 years) in which these events occurred. Five events involved demyelination, including 2 reports of optic neuritis, 2 reports of transverse myelitis, and 1 report of non-specific "demyelination". Reports of arthritic and hypersensitivity events are discussed in more detail below.

Reports of arthritic conditions were further investigated due to the theoretical concern that their

etiology may be analogous to the autoimmune pathogenesis hypothesized in naturally acquired Lyme disease. There were 13 reports coded as rheumatoid arthritis (RA), 74 reports coded as arthritis, and 46 coded as arthrosis. In general, reports are coded as RA if they mention "rheumatoid arthritis" as a diagnosis in the report. The coding term arthritis is used if the word "arthritis" or "arthritic" is used without further elaboration. Arthrosis is the selected code if the report mentions "joint swelling". Although it is possible for reports to be coded with all three of these COSTART terms, these counts are mutually exclusive in our analysis as we established a precedence of RA>arthritis>arthrosis for purposes of counting cases. Reports coded as RA, arthritis, and arthrosis would be counted only in the RA group. Similarly, reports coded as arthritis and arthrosis would be counted only in the arthritis group.

We examined these reports by age, gender, and dose. We found the median ages of the three groups to be similar (RA: 52 years, arthritis: 53 years, arthrosis: 54 years). However, there were more men than women for arthrosis reports (24 vs 15; 62% vs 38%); women predominated for reports of RA and arthritis (RA: 9 women, 4 men; arthritis: 39 women, 34 men). There was also a suggestion of an increased number of events after the second dose for reports coded RA (3, 8, 0, 0 for doses 1-4 respectively) and arthritis (25, 32, 12, 0) but not arthrosis (19, 15, 8, 1).

The finding of more reports of men with symptoms and signs coded as arthrosis is somewhat unexpected because the diagnosis of arthritis in the general population (which might include cases that are coded as arthrosis in VAERS) is more prevalent in women than men. The finding of more events coded as RA and arthritis reported as occurring after the second dose is unexpected because it is different than the pattern seen for all adverse events reported after LYMErix® (figure 3), in which more events are reported as occurring after the first dose.

We next examined the distribution of the time to onset of the adverse event, stratified by dose, to determine if the excess of RA and arthritis coded reports occurring after the second dose clustered in time. We found there was wide variability in time to onset with no temporal clustering as shown in figures 4 and 5.

If the first dose primed for an immune mediated reaction caused by the second dose, it might be expected that events following the second dose would occur in close proximity to receiving the second vaccine dose. The pattern we actually observed does not suggest this is happening. Since there is more time between the second and third doses (11 months) than between the first and second dose (1 month), the greater number of cases after the second dose that have been reported may be due simply to the increased amount of time during which a vaccine recipient can report an adverse event.

To further evaluate the three coding terms for arthritic conditions (RA, arthritis, and arthrosis), we reviewed the reports for data consistent with an inflammatory arthritis. We counted reports that gave evidence of joint pain, limited motion, joint tenderness, joint warmth, and joint swelling. The results are presented in table 3. We selected reports indicating joint swelling as most likely to be "true arthritis" and further evaluated them by examining the distribution of time to onset stratified by dose as shown in figure 6. This analysis revealed wide variability in time to onset with no temporal clustering.

We also closely examined reports of facial paralysis because of its association with Lyme disease and the theoretical possibility of autoimmune induced disease. There were 13 reports of facial paralysis with unknown etiology. Facial paralysis was reported in people aged 18 to 73 years with all but one person older than 50 years (median age 53 years). The reports included 10 men and 2 women, with one report not including gender. Nine cases occurred after administration of the first dose of

LYMErix®, and 4 occurred after the second dose. The predominance of men reporting this event was notable; an even number in each gender would be expected based on the natural history of the condition.

In October 2000, we conducted a telephone census (i.e. a survey of all available and willing individuals who submitted reports) of the 12 cases of facial paralysis that had been reported as of that date. We obtained additional information on 7 of the 12 cases of facial paralysis, but 5 reporters could not be contacted. Five of the seven completely recovered, with two suffering mild residual facial paralysis. Reporters were queried about risk factors for facial paralysis from 8 major categories including trauma, infections, metabolic diseases, neoplasms, toxins, iatrogenic injuries, and idiopathic causes. We found that 2 of 7 individuals reported a history of hypertension, another person reported both hypertension and diabetes mellitus, and a fourth had multiple cranial nerve palsies without a known etiology despite an extensive evaluation. This patient reported onset of headache requiring medical evaluation prior to vaccination, possibly representing the first symptom of neurologic illness. None of those surveyed reported active Lyme disease. In addition, 2 people reported concomitant administration of other vaccines (one with influenza, measles, tetanus and one with influenza alone), although no causal relationship between these other vaccines and facial paralysis has been established. We also examined the time to onset of these reports as shown in figure 7. This figure shows a wide spread in times to onset with a small peak at 4 weeks after vaccination that differs from the time to onset of all adverse events reported following LYMErix®.

Thirty-seven reports of possible hypersensitivity reactions were reported to VAERS. After review, 24 reports were identified that included either urticaria or respiratory symptoms following

LYMErix® administration. Twenty-two patients (10 women, 10 men, 2 of unknown gender) reported urticaria, and 2 women reported respiratory symptoms. In one these cases, a 39 year old woman developed a red face, itching, and had the sensation her "throat was closing" within one hour of receiving the second dose of LYMErix®. She was treated in an emergency room with epinephrine, steroids, and diphenhydramine and recovered. The second case was also in a 39 year old woman who, 9 hours after receiving the first dose of LYMErix®, experienced "itching, hives, chills, myalgia, and labored rapid breathing". She was also treated in an emergency room with epinephrine, diphenhydramine, prednisone, famotidine, and hydroxizine and recovered. Fifteen cases of urticaria were reported to occur after the first dose, 6 after the second dose, and 1 after the third dose. The close temporal proximity to vaccination of some of the reported cases, including 2 of the reports with respiratory and dermatologic symptoms, makes a causal link plausible.

The previously mentioned theoretical concern that there may be an autoimmune etiology of arthritis after LYMErix® has also raised the hypothesis that people with the DR4 HLA type may be potentially susceptible to developing this condition. Nineteen adverse events have been reported among vaccine recipients with a self-reported DR4 HLA type and 17 in individuals with other HLA types. We did not attempt to verify the reported HLA type. Reports of adverse events in people with the DR4 HLA type may be more likely to be reported to VAERS because of the theoretical concerns previously mentioned. As a result, it may be misleading to quantitatively compare the prevalence of HLA types among VAERS reports with that seen in the general population. More adverse events occurred after the second dose in people with DR4 HLA types as well as those with non-DR4 HLA types. When we examined the time to onset stratified by dose, we found that adverse events were reported to occur at a

wide range of time after vaccination, and no potentially informative clustering is observed. The increased number of reports of AE's after the second dose might reflect an increased observation time as previously discussed. The coding terms arthritis and arthrosis were more common in people who reported any HLA type than in all VAERS reports after LYMErix®. However, the coding terms and clinical characteristics of the reports were similar for both the DR4 HLA types and the other HLA types, and there was not a predominance of arthritic conditions in people reporting the DR4 HLA type. This might be because people with joint symptoms after LYMErix® are more likely to be HLA typed and have the results reported to VAERS.

A history of Lyme disease has also been raised as a possible risk factor for adverse events after LYMErix®, so we examined reports of adverse events in people with a self-reported history of Lyme disease. We did not attempt to validate the history of Lyme disease. Seventy-six adverse events were reported in people with a self-reported history of Lyme disease and the ten most common adverse event coding terms are shown in table 4. Review of these reports reveals no clear patterns suggesting a difference in adverse events for this group when compared with all people reporting adverse events after LYMErix® (table 1).

Finally, 16 individuals have reported Lyme disease after vaccination. We did not attempt to confirm these diagnoses. These reports describe symptoms and signs consistent with Lyme disease, and are different from other people reporting adverse events after LYMErix®. Fourteen of these adverse events were reported after the first or second dose, before the vaccine series was completed, so they may have not yet achieved an adequate immune response. A few reporters felt that the vaccine had caused the symptoms of Lyme disease because the symptoms continued despite adequate antibiotic

therapy. It is not possible to examine this hypothesis with data reported to VAERS.

Summary of Analysis of VAERS Data

Reports included adverse events found to be associated with Lyme vaccine in pre-licensure trials, including injection site reactions, transient arthralgia and myalgia within 30 days of vaccination, fever, and flu syndrome. For other reported adverse events, causal relationships with LYMErix® have not been established. Hypersensitivity reactions were reported to VAERS and some can be plausibly linked to the vaccine because of the short latency between vaccination and reaction onset. No clear patterns in age, gender, time to onset, or vaccine dose have been identified, although the unexpected predominance of reports of athrosis and facial paralysis in men may warrant further consideration. For reports containing information on HLA types, clinical descriptions of adverse events are similar in people with DR4 and non-DR4 HLA types and do not suggest more inflammatory arthritis in people reporting the DR4 HLA type. Characteristics of adverse events in people with a self-reported history of Lyme disease do not differ substantially from reports of all adverse events reported after LYMErix®.

Reports of the onset of Lyme disease or symptoms consistent with Lyme disease after LYMErix® have been reported to VAERS. Most occurred before completion of the recommended 3 dose series and may represent infection prior to the development of immunity. It is not possible to determine whether LYMErix® can reactivate Lyme disease based on passive surveillance reports received by VAERS.

Follow-up Studies

To further address the question of a possible link between LYMErix® and arthritis, the FDA is conducting a telephone survey of individuals who have reported arthritic conditions to VAERS after

receiving LYMErix®. This survey is a census of available and willing individuals who submitted reports that have been coded as arthritis, arthrosis, rheumatoid arthritis, joint disease, and arthralgia. The goal of the survey is to describe the characteristics of these adverse events, identify concomitant factors that might influence the characteristics of these events, and describe the relationship of the events to LYMErix® vaccination. After this survey phase of the study is complete, we will identify cases of arthritis and plan to conduct a VAERS-based case-control study to examine the hypothesis that Lyme vaccine causes arthritis.

We plan to compare people reporting arthritis after LYMErix® with 2 control groups. The first control group will be people reporting arthritis to VAERS after other vaccines. The second control group will be people reporting adverse events to VAERS other than arthritis after LYMErix®. All controls will be age, gender, and race matched with the case group. All three groups will be tested for DR HLA types at the allele level and for peripheral blood lymphocyte response to OspA and LFA-1. We will attempt to determine if people reporting arthritis after LYMErix® have a higher prevalence of certain HLA alleles that are known to be associated with rheumatoid arthritis and have the same third common hypervariable region, while simultaneously having greater peripheral T-cell reactivity to OspA and LFA-1. Given the relatively small number of arthritis cases reported after LYMErix®, probably only a very strong risk will be detectable.